

## Biomarker-guided personalised emergency medicine for all – hope for another hype?

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### Summary

Polymorbid patients, diverse diagnostic and therapeutic options, more complex hospital structures, financial incentives, benchmarking, as well as perceptual and societal changes put pressure on medical doctors, specifically if medical errors surface. This is particularly true for the emergency department setting, where patients face delayed or erroneous initial diagnostic or therapeutic measures and costly hospital stays due to sub-optimal triage.

A "biomarker" is any laboratory tool with the potential better to detect and characterise diseases, to simplify complex clinical algorithms and to improve clinical problem solving in routine care. They must be embedded in clinical algorithms to complement and not replace basic medical skills. Unselected ordering of laboratory tests and shortcomings in test performance and interpretation contribute to diagnostic errors. Test results may be ambiguous with false positive or false negative results and generate unnecessary harm and costs. Laboratory tests should only be ordered, if results have clinical consequences. In studies, we must move beyond the observational reporting and meta-analysing of diagnostic accuracies for biomarkers. Instead, specific cut-off ranges should be proposed and intervention studies conducted to prove outcome relevant impacts on patient care.

The focus of this review is to exemplify the appropriate use of selected laboratory tests in the emergency setting for which randomised-controlled intervention studies have proven clinical benefit. Herein, we focus on initial patient triage and allocation of treatment opportunities in patients with cardiorespiratory diseases in the emergency department. The following five biomarkers will be discussed: proadrenomedullin for prognostic triage assessment and site-of-care decisions, cardiac troponin for acute myocardial infarction, natriuretic peptides for acute heart failure, D-dimers for venous thromboembolism, C-reactive protein as a marker of inflammation, and procalcitonin for antibiotic stewardship in infections of the respiratory tract and sepsis. For these markers we provide an overview on physiopathology, historical evolution of evidence, strengths and limitations for a rational implementation into clinical algorithms.

We critically discuss results from key intervention trials that led to their use in clinical routine and potential future indications.

The rationale for the use of all these biomarkers, is to tackle, first, diagnostic ambiguity and consecutive defensive medicine, second, delayed and sub-optimal therapeutic decisions, and third, prognostic uncertainty with misguided triage and site-of-care decisions all contributing to the waste of our limited health care resources. A multifaceted approach for a more targeted management of medical patients from emergency admission to discharge including biomarkers, will translate into better resource use, shorter length of hospital stay, reduced overall costs, improved patients satisfaction and outcomes in terms of mortality and re-hospitalisation. Hopefully, the concepts outlined in this review will help the reader to improve their diagnostic skills and become more parsimonious laboratory test requesters.

**Key words:** *personalised medicine; emergency medicine; biomarker; proadrenomedullin; adrenomedullin; D-dimer; natriuretic peptides; troponin; procalcitonin; comprehensive effectiveness research*

### The ever changing medical setting – a small history of time

In the seventies, quality of medical care was considered to be good. Life-expectancy, for example in Switzerland, was around 70 years, less than 3% of the population was more than 80 years old. Average length of hospital stay was around three weeks, fee-for-service was the reimbursement system of choice and healthcare costs consumed around 5% of the gross national domestic product [1].

A minority of patients were admitted through the emergency department (ED) [2]. Community-acquired pneumonia (CAP) worldwide was susceptible to narrow-spectrum antibiotics and generally treated for two weeks or more, allegedly to avoid recurrence and antimicrobial resistance. Clinically suspected acute myocardial infarction (AMI) was confirmed electrocardiographically and by elevated circulating creatine kinase levels, and treated with

bed rest, oxygen, rhythm monitoring, sedatives and opioids. “Cancer” was typically considered to be a final diagnosis and pulmonary embolism was frequently diagnosed at autopsy only.

A large fraction of clinical knowledge for internists could be comprehensively summarised in a one volume textbook, such as *Harrison's Principles of Internal Medicine*. A doctor's ruling was considered to be “state of the art”, and legal aspects and malpractice insurance fees were negligible [3]. In 2015, quality of medical care is considered to be good. In Switzerland, life-expectancy is almost 85 years and among the highest in the world, with a doubling of the population older than 80 years as compared with four decades ago. Average length of hospital stay is around seven days, a case-based reimbursement system by diagnosis-related groups (DRGs) has been implemented and healthcare costs consume around 12% of the gross national domestic product [1].

EDs provide 75% or more of medical admissions of usually multimorbid patients with polypharmacy. “Door-to-needle” time has become a dominant benchmark to maximise outcome in an interdisciplinary setting that involves highly-skilled nurses, generalists and specialist physicians. Microbiological cultures are routinely plated to detect multiresistant organisms in patients hospitalised with CAP, who are treated with steroids [269] and antibiotics for a mean of less than 6 days and fewer complications, if procalcitonin (PCT)-guided [4, 5]. For chest pain, standard protocols demand the use of high-sensitivity cardiac troponin rapidly to rule-out or rule-in AMI for early revascularisation and monitoring in costly coronary or intensive care units [6, 7]. Clinical probability assessment and measurement of D-dimer in low- and moderate-risk patients should ensure that suspected pulmonary embolism can be safely ruled out, without the need for additional imaging [8, 9]. “Cancer” is not accepted anymore as a “final” diagnosis. Molecular subtyping on a cellular level, detailed radiographic staging and customised oncological therapy with monoclonal antibodies are routinely performed. This yields, overall, a superior cure and survival rate for “malignant” tumours as compared with diseases previously considered to be more “benign”, such as congestive heart failure (CHF).

Today, as you read this review in PDF format online, it is – at least in part – updated by more timely and widely accessible information on the internet. Expectations of society regarding healthcare have markedly increased. Patient safety drives international efforts to measure and publish the rate of errors and error-related harm. [3] One-third of patients recall a diagnostic error that affected themselves, a family member, or close friend [10] and 55% of surveyed patients listed a diagnostic error as their chief concern when seeing a physician [11]. Malpractice claims against US internists are most frequently due to errors in diagnosis and consequent suboptimal therapy and patient outcome [12].

Apparently, today we perceive a more urgent need for a safe and efficient, but even more personalised, approach of routine medical and nursing care to patients with common complaints. With this aim, laboratory tests can be of help if the indication for ordering is not excessive and unselected but is based on rational criteria. Their performance

should be validated in randomised controlled trials in settings appropriate for routine care. The often misinterpreted term “biomarkers” refers to their role as specific markers of biological processes in a given disease state. This is the rational foundation for the belief that they have high potential to individualise clinical care with improved risk stratification, site-of-care decisions, diagnosis and treatment selection. This is not only for selected individuals with neoplastic cases but for common diseases in an everyday patient, therefore providing routine personalised emergency care for all.

## Personalised emergency medicine – from clinically selected individuals to risk-adapted standard of care

The term “personalised medicine” suggests an approach to care that is based on individuals rather than groups. This is not a new concept *per se*. Since ancient times, caregivers considered individual characteristics such as age, co-existing conditions, preferences, and beliefs in crafting a personal management strategy. The term personalised medicine became fashionable again with the recent use of individual genomic information in prescribing an expensive and side-effect prone therapy, such as customised monoclonal antibodies in oncology or abacvir for HIV treatment. Thereby, the genetic signature of a patient predicts treatment success or failure or allergic complications and has thus cost-considerations. Testing for human epidermal growth factor receptor type 2 (HER2) helps selection of breast cancer patients who will benefit from trastuzumab [13]. Testing for the KRAS mutation helps selection of patients most likely benefiting from therapies inhibiting the epidermal growth factor receptor [14]. Sequencing of whole genome, the epigenome, transcripts, microRNA, respectively, proteomics or metabolomics have the potential for further improved diagnostics, prognostic assessment, therapeutic targets and stratified treatments for cancer and rare disorders. However, these tools are costly and time-consuming and, therefore, not readily available as point-of-care test for early risk stratification in the emergency setting. In addition, to date individual genomic variants have variable penetrance and minor impact in common illnesses, such as cardiorespiratory diseases. For example, currently available genetic tests add no additional clinical useful information in guiding anticoagulation [15] or cardiovascular risk profiling. For these reasons, the vast majority of acutely ill patients, such as the masses treated in the ED, do

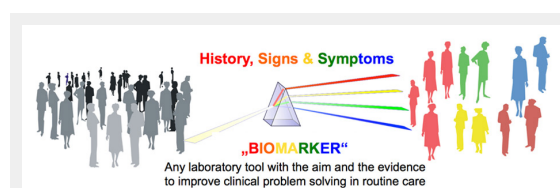


Figure 1

Combined clinical and biomarker assessment for a personalised emergency triage, therapeutic intervention and site of care decisions.

currently not benefit from stratification by tests on the genetic or molecular level.

In contrast, blood circulating biomarkers play an important role in the current diagnostic work-up of ED patients. A biomarker may be defined as any protein or other macromolecule that can be objectively measured and evaluated as an indicator of normal biological processes, pathological processes, course of diseases or pharmacological responses to a therapeutic intervention. Readily measurable biomarkers provide important information about aetiology of a disease, and the need for interventions and prognosis. *Diagnostic* biomarkers confirm the presence or absence of a disease. Thereby, biomarker results need to be interpreted in the context of the pre-test probability and cut-off ranges are to be preferred to dichotomous and overly simplistic cut-offs. A high specificity and a high positive predictive value is required to “rule in” a disease (e.g. a PCT level of 0.5 ng/ml to prescribe antibiotic therapy in respiratory tract infections). Conversely, a high sensitivity and a high negative predictive value is needed to “rule out” a disease (e.g., a PCT level of 0.1 µg/l to withhold antibiotic therapy in infections of the respiratory tract [table 1]). In between there is a grey zone where the biomarker alone does not add sufficient information for a final ruling. *Monitoring* biomarkers should mirror effectiveness of therapy for the purpose of titration (e.g., BNP in the treatment of congestive heart failure or PCT for antibiotic duration). *Surrogate* biomarkers should correlate with clinical outcome in the setting of an therapeutic intervention (e.g., HbA<sub>1c</sub> as surrogate for complications of diabetes). *Stratification or staging* biomarkers classify diseases based on outcome probability, for example to limit side-effects of aggressive therapies to high-risk patients with poor disease outcome if untreated (e.g. D-dimer to exclude venous thromboembolism in need for anticoagulant therapy in patients with a higher bleeding risk). *Companion* biomarkers identify patients most likely to benefit from a specific therapy (e.g. toxoplasmosis serology, quantiferon testing in HIV, HER2 positive breast cancer better selects women with breast cancer for treatment with trastuzumab [Herceptin®]).

Biomarkers should expedite the correct diagnosis and treatment leading to personalised and tailored therapy [16] (fig. 1). In emergency patients with cardiorespiratory symptoms, patient history, clinical examination, chest radiographs in conjunction with specific biomarker levels provide important information useful for the fast and accurate management of the patient. Point-of-care tests with fast turnaround times can already deliver this information in the prehospital setting including general practices and ambulances which may further improve the management of multimorbid and elderly patients with unspecific complaints [17–20].

Biomarkers, may also improve site-of-care decisions which are pivotal and major cost drivers. Decisions to hospitalise patients admitted to the ED are often based on “gut-feeling” of healthcare providers, patients or relatives rather than objective clinical information. A recent survey involving lower respiratory tract infection (LRTI) patients revealed that, independently of expected mortality based on pneumonia severity index or CURB-65 scoring, most LRTI patients are hospitalised because physicians, nurses,

patients and relatives all believe that inpatient management is indicated for medical reasons, particularly fear of severe infection. Nursing reasons and patients’ and relatives’ personal preferences were mentioned to a lesser extent [21].

### Clinical skills in emergency medicine – Osler’s “science of uncertainty and art of probability”

As students we were taught to collect signs and symptoms and try to fit them in a common physiopathological entity characteristic of a particular disease. This systematic approach with thorough history-taking and physical examination allows one to combine the mosaic fragments of cough, dyspnoea and/or chest pain to frame common clinical diagnoses, such as ACS, pulmonary embolism, acute heart failure (AHF) or CAP. Based on clinical reasoning we initiate more or less specific and targeted therapies, such as revascularisation, thrombolysis, diuretics or anti-microbial drugs. This heuristic strategy, while being efficient, relatively resource-sparing, and generally accurate, is not without fail [22].

Seven decades ago, history-taking alone allowed the allegedly correct diagnosis known these days to be made in 74% of sick patients, usually in later stages of their disease [23]. More recently, medical history and physical examination was presumed to yield a correct final diagnosis in more than half of cases [24]. A Hawthorne bias makes these study figures likely to be overly optimistic. Indeed, a more recent analysis of dyspnoeic patients under ED conditions revealed the correct diagnosis in only 41% after history taking, which was not improved after lung auscultation. Notably, this number varied from 100% (smoke inhalation) to less than 10% (chest wall pain) [25]. In real-life, clinical performance depends largely on skills and experience, and the quality of teaching and supervision of junior doctors [22]. Senior physicians, are given little time or financial incentives for teaching duties and teaching is not an intuitive endeavour for all physicians [26]. Sleep deprivation and circadian rhythm disruption in doctors are strongly associated with human error and harm [27].

The clinical judgment even of experienced doctors can be impaired by cognitive biases, such as availability, anchoring, premature closure and framing. Physicians underestimate their inter-person variability for clinical diagnosis and overestimate their *kappa* (i.e., the agreement with an independent colleague), even in the presentation of allegedly “easy to diagnose” common diseases. [28] For example, there is a dismal inter-physician agreement about signs of chest examination: the *kappas* for cyanosis, tachypnoea, and whispered pectoriloquy were only 36%, 25% and 11% (with 100% being perfect agreement) [29].

On average, medical patients are more than 70 years old on hospital admission. Most emergency physicians have not been trained in specific geriatric approaches, and many report being less comfortable when dealing with older patients [30]. Masked (e.g., absence of fever) or unusual presentation of disease in poly-morbid, elderly patients, or limited patient cooperation (dementia, delirium, uncooperativeness or deception) can be contributory [19].

Patterns of presenting complaints of patients vary in cardiorespiratory diseases, including typical local symptoms such as cough, at times productive, dyspnoea, chest pain to

systemic moans such as fatigue, anorexia or myalgia [31]. Physical signs are not always present and, if present, may be difficult to elicit when examining the chest [31]. Reports on the validity of such signs have shown considerable disagreement among physicians, leading to unreliable clinical observations in cardiorespiratory diseases [29, 32, 33]. Indeed, clinical signs and symptoms show at best a moderate helpful in the differential-diagnosis in patients with acute dyspnoea [34]. Dullness to percussion, changes in the intensity of breath sounds, and inspiratory crackles may be present in a variety of pulmonary diseases that cause lung stiffening, including AHF, pulmonary fibrosis and obstructive lung disease [25]. Presence of sputum or its discolouring, dyspnoea, crackles, fever and increased white blood cell count are insensitive and unspecific parameters for the diagnosis of bacterial LRTI requiring antibiotic therapy [28, 35, 36].

### Laboratory medicine and circulating biomarkers—friend or foe to clinicians?

This review focuses on the use of readily available “personalised information” from biomarkers for improved diagnosis and prognosis of common acute diseases, namely cardiovascular and thromboembolic diseases, and infections. Biomarkers for which randomised controlled intervention trials in the emergency setting are available were selected.

Following emergency admission of patients with cardiorespiratory complaints, history taking and physical examination result in a first list of differential diagnoses based on subjective likelihood assumptions. For example, an afebrile elderly patient presenting to the ED with dyspnoea as leading complaint, cough and pressure on the chest (or was it pain?) might suffer from AHF, AMI, CAP with pleuritis or even pulmonary embolism.

In the past, laboratory tests were used to identify organ and system dysfunctions or diseases to confirm initial impressions or rule out alternative diagnoses. While this is still true, testing today is used more and more for prognostication, risk stratification, site-of-care decisions to reduce hospital readmissions [37–40]. Today, most cardiorespiratory diagnoses are not considered final until after laboratory testing is complete [41, 42].

The physicians’ increasing reliance on objective data from diagnostic testing is arguably, at least in part, due to reduced or neglected history and physical examination skills [26, 41]. Importantly, a skilled clinical judgment after focused history-taking and physical examination remains a pre-requisite to minimise testing-related diagnostic errors. Importantly, physicians should not make decisions based upon one isolated finding, but rather on the overall *gestalt* of the patient’s illness. Thereby, clinical reasoning is essential to determine the pre-test probability of a disease (i.e., prevalence), of treatment failure or complication and for adequate interpretation of laboratory test results. As there is ambiguity about what constitutes disease, more testing will produce more “abnormal” findings, resulting in further testing, which in the end makes patients sicker (and poorer) [43]. It leads to unnecessary worries, procedures, treatments and potentially unnecessary hospitalisations and harm. Conversely, false negative test results lead to under-

estimation of disease status, delays and possibly worse outcome [41].

The physician’s role in emergency medicine has changed from clinical problem solving by history taking and examination alone to determine the pre- and post-test probabilities essential for the ordering and interpretation of laboratory tests. Misapplication of test results can result from misinterpretation by the clinician – either from misunderstanding the clinical implications of a result or from not understanding the limitations of the test methodology (i.e., statistical variations, performance limitations, or interfering substances) [41]. Therefore, clinical skills of experienced physicians need to be synergised with modern biomarker strategies knowing strengths and limitations of both.

Thanks to advances in quality control, diagnostic errors today are rarely the result of an error in the analytical test itself. Overall, it is estimated that laboratory results are misleadingly wrong in 2%–4% of cases; roughly the same error rates are found in diagnostic radiology [41]. Most laboratory-related errors now originate from the pre-analytical and post-analytical processes, namely issues related to the physician ordering and interpreting of test results. Lapses in the reliable communication of abnormal laboratory and imaging results is a problem, even in systems with advanced electronic medical records [41, 44]. In daily routine the time between the initial clinician-patient encounter, test order, receipt of the sample by the laboratory, the test result availability and clinician action based on results is considered too long by many. Point-of-care testing should minimise testing-related delays provided the quality of the assay, namely sensitivity, is not impaired [45, 46].

There is a true need of evidence-based medicine criteria in laboratory medicine. The challenge to address for scientific investigators is the difficulty to design methodologically rigorous randomised double blind trials without limiting their validity for real-life, namely in the emergency setting. Trials are performed on novel markers rather than established markers. The established markers are mostly indirectly tested as the control arm in studies investigating novel markers. The superiority of the novel markers in such trials may also result from the fact that patients in the biomarker arm are treated and managed by standard operation procedures whereas the control arms are mostly usual care. It may hence be that these studies demonstrate the superiority of patient management by standardized operating procedures (SOP) rather than superiority of patient management by a novel biomarker.

Physicians often disagree about what inappropriate laboratory utilisation is [47]. Unfortunately, many “routine” laboratory tests are being ordered in “bundles” without any impact on diagnostic or therapeutic management. This creates needless traumas of venepuncture and unwarranted prescriptions are a colossal waste of money – an unresolved problem also at our own hospital. Many house staff continue to order recurring laboratory tests (“daily labs”). Multiple teams of physicians often consult on a single case, write multiple sets of phlebotomy and laboratory orders – often duplicated. Blood draws should not be considered innocuous: up to 20% of hospitalised patients with acute myocardial infarction suffered from phlebotomy-related



hospital-acquired anaemia with an haemoglobin level of <11 g/dl [48].

The elimination of unnecessary tests and procedures has been identified as a key factor to reduce the trauma and expenses of hospitalisation [49]. The American Board of Internal Medicine's "Choosing Wisely" campaign to reduce unnecessary and potentially harmful tests is an important first step [50]. Unbundling of tests, supervision by senior physicians, feedback of individual phlebotomy-rates, and warnings in electronic order entry systems lead to a reduction of phlebotomies of 20 to 60% [51, 52]. Unfortunately, these laudable attempts are usually labour intensive and short lived, initially promising effects disappearing shortly after cessation of the educational effort [52]. Efforts incorporating education, requisition design, and funding incentives have demonstrated the most durable effect [43].

## Personalised triage in the ED using risk scores & biomarkers

Hospital EDs are increasingly appreciated by patients for their high-intensity medicine around the clock and are overwhelmed by patients with both urgent and non-urgent problems [53, 54]. This leads to overcrowded ED waiting rooms with long waiting times. As a consequence, patients truly needing urgent care may not be treated in time, where-

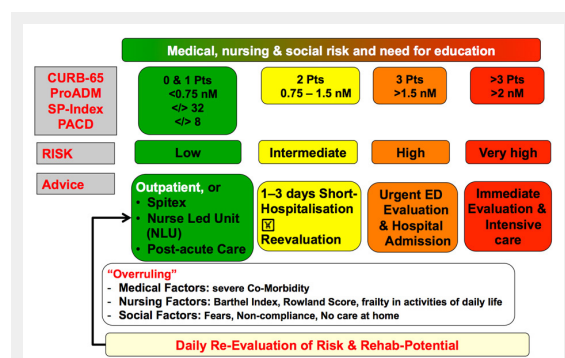
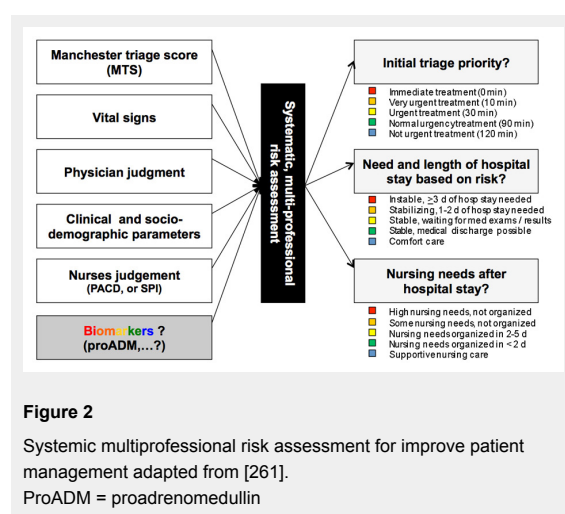
as patients with non-urgent problems may unnecessarily receive expensive and oversized emergency care. Time to effective treatment is among the key predictors for outcomes across different medical conditions ("time is cure"), including patients with AMI ("time is muscle") [55], stroke ("time is brain") [56], CAP [57] and septicemia ("surviving sepsis campaign") [58]. In the latter case, early initiation of fluid resuscitation and of appropriate anti-microbial improves outcomes [59–62]. In contrast, other adjunct sepsis therapies such as immuno-modulatory antibodies or tight glucose control have not proven to be beneficial [63, 64].

Emergency medicine is under continuous pressure to improve the value of healthcare services delivered. Physicians have an obligation to their patients and to society in regard to high quality, but also cost-effectiveness. The complexity of increasingly multimorbid patients with acute exacerbations of their chronic diseases is more challenging than ever. Medicine has become more technical and complex leading to system-related errors, such as technical failure, equipment problems and organisational flaws.

For these reasons, an accurate and well-validated triage system in the ED is pivotal for an optimal initial triage of medical patients. ED triage should not only focus on treatment priority, but also on site-of-care decisions (i.e., outpatient versus inpatient management) and early identification and organisation of post-acute care needs. An appropriate risk assessment and subsequent triage is crucial for an optimised patient care and allocation of limited healthcare resources. For this purpose, tools have been propagated, namely standardised triage scores for the ED, nursing scores to predict post-acute nursing care needs and biomarkers thought to mirror physiopathological changes and severity of disease (fig. 2).

Many patients prefer outpatient treatment [65]. Admission rates and length of stay are affected by a variety of medical, functional, psychosocial factors including patient and relatives preferences [66–69]. Consecutively, despite a low-risk according to clinical severity scores per se, many patients are still hospitalised for medical co-morbidities and psychosocial reasons [66, 67].

Community-acquired LRTIs include acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease and CAP. They are among the most frequent causes of hospitalisation [70] and direct treatment costs amount to \$15 billion in the USA [71]. Inpatient care of CAP is 8 to 20 times more expensive [66, 72] and carries a higher risk of nosocomial infections including *Clostridium difficile*-associated diarrhoea [73] than outpatient treatment. In the multicentre ProHOSP study, compliance with the PCT guided antibiotic algorithm was 90% [74]. Importantly, only half of the patients with LRTI in the low medical risk groups as determined by PSI or CURB65 were treated as outpatients despite high intensity implementation [74, 75]. Regardless of low observed risk for adverse events, fear of medical complications was the dominant motive for hospitalisation similarly among physicians, nurses, patients and relatives [21]. Thus, clinical severity scores, despite being recommended in guidelines, have been insufficient in clinical application due to complexity, problems memorising, but also because of both relative insensitivity and non-specificity



**Table 1:** Commonly used biomarkers to personalise medicine in the emergency triage with indications and limitations.

Biomarker Assay technique	Common clinical setting	Cut-off ranges (may be assay specific)	Further reading	Rule-in	Caveats in ruling-in (false high, impaired specificity)	Rule-out	Caveats in ruling-out (false low, impaired sensitivity)
Proadrenomedullin (ProADM) Fluorescence Immunoassay	Risk stratification in respiratory tract infections in the ED	<0.75 µg/l low risk 0.75–1.5 µg/l intermediate >1.5 µg/l high risk	[39] [261] [262] [263]	More intensified monitoring and treatment	Social and nursing aspects of hospitalisation	Outpatient treatment	Perceptions and preferences of patient and relatives Other important comorbidities
D-dimer Highly sensitive rapid ELISA, nephelometric or turbidimetric assays	Venous thromboembolism (VTE)	<500 µg/l: no imaging if low or intermediate (unlikely) clinical probability for VTE Imaging recommended if ≥500 µg/l independent of D- dimer if high VTE probability Patients >50 years: consider age-adapted cut- off ranges: cut-off = age x 10	[167] [264]	Anticoagulation if VTE ruled in by imaging.	Age ≥80 years, all conditions associated with enhanced fibrin-turnover: e.g., systemic inflammation, vascular dissections, infection, trauma, cancer, pregnancy, inpatients	Consider alternative diagnosis to VTE, e.g., aortic dissection	High clinical probability for VTE, upper-extremity deep vein thrombosis, pregnancy
High sensitivity cardiac troponin T or I (hsTp) hsTpT: e.g., electro- chemiluminescent immuno assay (ECLIA) hsTp I: e.g., luminescent oxygen channelling assay (LOCI)	Suspected acute coronary infarction (AMI)	hs-cTnT <14 ng/l low risk 14–52 ng/l intermediate >52 ng/l high risk	[265, 266]	AMI	Myocardial wall stretch and cell necrosis of non- ischaemic origin (e.g., Tako tsubo, pulmonary embolism, myocarditis), demand ischaemia (e.g. sepsis) persistently elevated level up to 14d, renal failure	Consider alternative diagnosis to AMI, conservative therapy of symptoms and cardiovascular risk factors	Time-lag of 1 to 3 h, rarely circulating antibodies against analyte
B-type natriuretic peptide (BNP) or N-terminal fragment of BNP (NT-BNP) or MR- proANP Luminescent oxygen channelling assay (LOCI)	Dyspnoea and / or suspected acute heart failure (AHF)	BNP: <100 ng/l AHF unlikely 100–400 ng/l intermediate >400 ng/l AHF likely NT-BNP: <300 ng/l AHF unlikely 3 age-dependent cut-offs for rule-in of AHF (450, 900, 1800)	[131] [136]	AHF	Age, ACS, myocardial hypertrophy, myocarditis, pulmonary hypertension, stroke NT-BNP: renal failure	Consider alternative diagnosis to AHF	Obesity, flash pulmonary oedema, mitral valve disease, pericardial tamponade or constriction, BNP: limited stability of analyte
High sensitive C- reactive protein (hsCRP) Nephelometric assay, latex enhanced turbidimetry and various immunoassays	Cardiovascular risk profiling Inflammatory status	Cardiovascular risk: <1 mg/ l: low 1–3 mg/l: intermediate 3.1–10 mg/l: high  Inflammatory status <20 mg/l: low 20–50 mg/l: intermediate >50 mg/l: high	[267, 268]	Cardiovascular risk: Statins for primary prevention in the GP setting for antibiotic stewardship in RTIs	Inflammatory acute-phase response of concomitant, non-infectious disease (e.g. SIRS, cancer, thromboembolic disease)	SIRS	Cardiovascular risk: contribution of other cardiovascular risk factors Time-lag to peak response (-72h), steroids, hepatic failure
Procalcitonin (PCT) Fluorescence immunoassay	Antibiotic Stewardship in Infections , namely of the respiratory tract in ED and hospital ward antibiotic stewardship; Infectious aetiology of SIRS in the ICU	ED & hospital ward: <(0.1)–0.25 µg/l bacterial infection (very) unlikely; >0.25 (0.5) µg/l ng/ml bacterial infection (very) likely  ICU: <(0.25)–0.5 bacterial infection (very) unlikely; >0.5 (1.0) ng/ml bacterial infection(very) likely	[84] [177] [197]	Prescribe antibiotics in LRTI in the ED and hospital –ward setting. In the ICU setting escalation of antibiotic therapy based on serial PCT measurement not recommended	New-borns, children, severe trauma and systemic inflammation malaria, medullary thyroid cancer and paraneoplastic hormone production	Evaluate alternative diagnosis to systemic bacterial infection, discontinue antibiotics in LRTI and sepsis,	Early-course (24h) , sub- acute, and localised infections, insensitive assay, should be applied in conjunction to clinical improvement

AB = antibiotic; AHF = acute heart failure; ED = emergency department; GP = general practitioner; ICU = intensive care unit; PCT = procalcitonin; SIRS = systemic inflammatory response syndrome; USA = United States of America; VAP = ventilator-associated pneumonia

for outcomes [76, 77]. Most deaths in patients with low risk scores are non-CAP-related [76], and most causes of re-admission within 30 days are due to co-morbidities (74%)

rather than CAP (20%) [78]. A further limitation of most clinical risk scores for LRTI is that they are only validated for CAP.

**Proadrenomedullin (ProADM) – “runner up” for a more personalised site-of-care decisions**

Adrenomedullin is a 52 amino acid polypeptide showing sequence homology with other calcitonin-related peptides. It was discovered 20 years ago as a secretion product of a pheochromocytoma [79]. The adrenomedullin gene encodes for a 185 amino acid prepropeptide, post-transcriptionally cleaved to produce the bioactive, amidated adrenomedullin. [80] Adrenomedullin, calcitonin-gene-related peptide (CGRP) and PCT belong to the same calcitonin peptide superfamily and emerge from different CALC genes with teleologically related, yet distinct physiopathological molecular regulation and effects [81–84]. These peptides are prototype “hormokines” which show behaviour of both hormones and cytokines and are ubiquitously hyper-expressed during the host response to bacterial infections [85–87].

Adrenomedullin and other calcitonin-peptides compete for binding to the same receptor family with agonistic and antagonistic properties [83, 88]. They exert their effects via G-coupled seven-transmembrane calcitonin receptor-like receptor in association with RAMP2 or RAMP3 to form the adrenomedullin receptors 1 and 2, respectively [89, 90]. Upregulated by hypoxia, inflammatory cytokines, bacterial products and shear stress, adrenomedullin acts systemically and in autocrine and paracrine fashion [91, 92]. Adrenomedullin is a very potent vasodilating agent believed to play a physiological role in arterial pressure homeostasis with additional immune modulating and metabolic properties [90, 93, 94]. Pleiotropic effects of adrenomedullin have been described: in tumour growth, neovascularisation, endothelium protection, bronchodilation, fertility, and immunity [95–99].

Adrenomedullin is found in plasma in health and at elevated concentrations during various pathologic conditions, including cardiovascular and renal disorders, sepsis, cancer and diabetes [90]. Based on the hormone’s biological importance and effects, the utility of measuring adrenomedullin in blood seems evident. However, abundant binding to peripheral and local receptors, a short half-life, and *ex vivo* physical characteristics including instability and “stickiness” make circulating adrenomedullin difficult to reliably directly quantify [100, 101]. During adrenomedullin’s processing into a mature hormone, it and an adjoining peptide, mid-regional proadrenomedullin (MR-ProADM; referred to here and elsewhere as proadrenomedullin [ProADM]), are cleaved off of the precursor in a 1:1 ratio. This stoichiometric secretion, the peptide’s apparently minimal if any biological activity and hence, binding, and its considerable chemical stability render ProADM an easily and robustly quantifiable surrogate biomarker for adrenomedullin [100, 102, 103]. ProADM has been used as a prognostic marker, alone or in risk stratification with other hormonal propeptides in patients with sepsis and severe pneumonia [82, 104, 105].

Adding prognostic biomarkers to a thorough clinical and interdisciplinary assessment bundles may allow detecting subgroups of patients with higher than anticipated risk requiring expedited assessment, intensified care and monitoring. Conversely, the prediction of a very low risk of adverse events by both interdisciplinary assessment and biomark-

er embedded in a system of risk-appropriate sites of care (e.g. nurse-led care NLC), structured discharge planning, patient education and immediate follow-up and an anticipated lower risk of healthcare associated infections [106] should provide sufficient confidence for physicians, nurses, patients and relatives in our risk-adapted triage with expedited discharge planning. Also, prognostic markers may help to select specific medical therapies for patients most likely benefiting from them, namely in resource-deprived settings (e.g., busy shifts and/or shortage of ED staffing).

Multiple “promising” prognostic biomarkers have been proposed in observational studies. Yet, the clinical efficacy and safety of their use for prognostication needs to be established in randomised-controlled intervention studies. C-reactive protein (CRP), PCT and other routinely measured markers have at best a moderate prognostic utility in systemic infections and other diseases [105, 107–109]. Thus, they cannot be used for site-of-care decisions. For prognostic purposes, ProADM has proven to be superior to CRP, PCT or any other of the plethora of marker from different biological pathways [105, 110–112]. In patients with CAP and other LRTI, proADM levels measured on admission were significantly associated with disease severity and fatal outcome [93, 111] ProADM had a superior prognostic value for predicting complications in LRTI compared to guideline-recommended clinical severity scores [104, 105, 113–120]. The combination of biomarkers and clinical scores (i.e., CURB65 and PSI) provided superior prognostic accuracy providing an additional margin of safety [105, 116, 117, 119, 121]. Consequently, an improved assessment of LRTI has been proposed based on CURB-65 and ProADM cut-off levels where patients were stratified into three risk classes with estimated mortality rates ranging from 0.65% to 9.8% (fig. 3) [121]. In a recent randomised-controlled pilot study this combined algorithm tended to reduce hospital length of stay without negatively affecting patient outcomes compared to patients stratified according to CURB-65 alone [40]. These results must be interpreted in light of unresolved organisational challenges in discharge planning and availability of beds in nursing homes and other post-acute care settings beds.

In the current society, patients and physicians are risk-averse and appear to prefer objective risk numbers compared to more complex clinical algorithms. Herein, ProADM alone or in combination with a prognostic biomarker bundle has the potential to enhance the interdisciplinary risk assessment and may improve the currently limited compliance with existing guidelines. This may also provide a more individualised and comprehensive risk assessment. Prognostic biomarkers may facilitate selection of patients for whom early discharge is safe and may help to focus resources to the patients in need. Prognostic biomarkers may help physicians to identify patients who would, and would not, benefit from distinct therapies and thus may allow a transition from bundled care to more personalised approaches, which in turn could result in improved patient outcomes.

## Personalised medicine in cardiology

### Cardiac troponin (cTn) in AMI

Acute myocardial infarction (AMI) is the cause of death in more persons worldwide than any other disease [122, 123]. With effective treatment in our hands, accurate and rapid diagnosis is of major medical and economic importance. In the initial assessment, electrocardiography (ECG) is of paramount importance to detect diagnostic ST-elevations which require immediate transfer to a catheter lab. There is no need to wait for the biomarker results. Still, cardiac troponin is measured to use it to 1) determine infarct size and 2) definitely prove that an AMI has occurred. Also, not all ST-elevations are unequivocal, as multiple causes other than STEMI might lead to ST-segment elevations such as left ventricular hypertrophy, myocarditis, takotsubo cardiomyopathy, and unknown causes as in healthy young men [124]. In suspected unstable angina and non-ST-elevation myocardial infarction (NSTEMI) cardiac troponins are indeed mandatory in all patients to decrease the diagnostic ambiguity of the clinical diagnosis. In a study setting, experienced primary care physicians correctly classified 88% of low-risk walk-in patients with chest pain as having either an organic or non-organic aetiology solely on the basis of their initial clinical judgment and before ordering any diagnostic tests [125]. In an ED setting with multimorbid patients and a higher pre-test probability for organic disease the ambiguity of clinical findings is much higher, for example >90% in a real-life study under emergency conditions [25]. Therefore, cTn testing is recommended by all current guidelines to improve clinical performance.

With the development of sensitive assays depicting either cTnI or cTnT (the only current biomarkers thought to be unique to the heart) the diagnosis of AMI was revolutionised [123, 126–128]. In a patient presenting with chest pain, a rise in cTn has become a *conditio sine qua non* for the clinical diagnosis of AMI. Cardiac troponins are our current gold standard for the detection of myocardial necrosis. The more sensitive the cTn assay used, the smaller the number of dying myocardial cells necessary for this signal to get detected. This has enabled patients to be detected even with very small AMIs. It also allows more rapid detection of AMI (usually within 1 or 2h if high-sensitivity cTn assays are used) [127]. Overall, high-sensitivity cTn assays seem to constitute a major medical and economic improvement in clinical practice.

However, the clinical use of these assays has created also challenges and uncertainties: It is unclear, whether the medical benefit observed in previous RCTs for early revascularisation and aggressive antiplatelet therapy also applies to patients with very small AMIs. As these patients still seem to be at an increased risk of death as compared to patients without elevated high-sensitivity cTn levels, the current ESC guidelines encourage us to do so [122, 123, 126–128]. Secondly, myocardial damage is not restricted to AMI, but may also accompany other medical conditions like septic shock, pulmonary embolism, hypertensive heart disease accompanying end-stage kidney disease, or acute heart failure. As we currently lack a biomarker that reliably detects plaque rupture or coronary thrombosis, we are often left with our basic clinical tools including patient history

to differentiate AMI from other causes of myocardial damage. The interpretation of cardiac troponin as a quantitative marker of cardiomyocyte damage, where the likelihood for the presence of AMI increases with increasing levels of cardiac troponin, and the use of absolute changes within 1–3h as complementary information to distinguish causes of chronic elevations such as heart failure (usually not showing relevant short-term changes) from causes leading to acute cardiomyocyte damage such as AMI, which are associated with a rise and/or fall. Third, once a diagnostic test is declared “gold standard”, it becomes practically impossible to definitely rule out false positive test results. This is currently the case with cTn. We strongly think that the heart is invariably the exclusive source of cTn elevations, regardless of the specific patient condition. However, as both the ECG and imaging techniques have by far lower sensitivity for myocardial necrosis as cTn, scientific proof often cannot be delivered in an individual patient. One easy option to exclude analytical false-positive levels is to measure a second cTn assay (e.g. cTnI when initially using cTnT). Fourth, despite the introduction of highly sensitive assays, follow-up measurements after 3 hours are needed to exclude AMI, which may delay time to ED-discharge. The use of assay-specific early algorithms [129], or the combination of cardiac troponin with copeptin, seem to allow an even earlier rule-out [130].

### Natriuretic peptides (ANP, BNP) in heart failure

For example, in a meta-analysis identifying the symptoms, signs, and tests most useful in diagnosing acute heart failure (AHF), no single history-taking or physical examination findings provided adequate discrimination [131]. The most discerning features of AHF – such as the presence of paroxysmal nocturnal dyspnoea, an S3 gallop, or jugular venous distention – have such a low incidence (each documented in <50% of patients with AHF) that their sensitivity for the diagnosis of AMF is low. In fact, the best single predictor of AHF was found to be a B-type natriuretic peptide (BNP) value of 250 ng/l with a sensitivity of 89% and a specificity of 81%. Nevertheless, high initial clinical suspicion (based upon the complete history and physical) was the most predictive element in the diagnosis of AHF. These observations highlight the need to interpret BNP levels as quantitative markers of hemodynamic cardiac stress. Low levels (<100 ng/l) are helpful for the rule-out of AHF as the cause of acute dyspnoea, while high levels (>400 ng/l) are helpful for rule-in of AHF. Based on data from several RCTs, natriuretic peptides (BNP, NT-proBNP, or MR-ProANP) should be obtained in all patients presenting with acute dyspnoea to the ED.

Accurate biomarkers of heart failure are highly desirable tools for physicians to either improve their ability make an early and accurate diagnosis or to follow positive or negative changes as a result of therapeutic intervention. The ability of physicians to make earlier diagnoses is valuable because therapeutic interventions are available that can make a significant impact on patient quality of life and cost of care [16, 132–137]. Annual costs of heart failure in Europe and the United States are estimated at \$130 billion, 70% of which is due to hospitalisation. Half of heart failure patients are re-admitted within 6 months and 10% are re-ad-



mitted twice with heart failure [16, 134]. Fewer re-admissions by guided therapy methods could significantly impact the costs associated with this prevalent disease. All three clinically available natriuretic peptides (BNP, NT-proBNP, or MR-ProANP) seem to have similar diagnostic accuracy in this indication [16, 38, 132–143]. In addition, natriuretic peptides, as quantitative markers of heart failure that summarise the extent of systolic and diastolic left ventricular dysfunction, valvular dysfunction, and right ventricular dysfunction [136], provide valuable information for risk stratification in patients with acute and chronic heart failure [38, 140–143]. Although still under some debate, BNP and NT-proBNP measurements also seem capable of improving the long-term management of patients with chronic HF [141, 142]. Detailed recommendations on how to best apply these biomarkers have recently been provided in this journal [136]. Appropriate cut-off values have been defined in large observational studies, and evidence from large randomised controlled studies confirms both medical and economic benefit from their use.

The use of natriuretic peptides shares one important challenge comparable to that of cTn: Having become the most sensitive test to detect a disorder (heart failure), other current clinically available methods including cardiac imaging have a major limitation in the clarification of unexpected and potential “false positive” elevations of natriuretic peptides. Again, one easy option to exclude analytical false-positive levels is to measure a second natriuretic peptide (e.g. NT-proBNP when initially using BNP).

## Personalised medicine in venous thromboembolism

### D-dimers

For many years, the diagnosis or exclusion of acute venous thromboembolism (VTE), defined as deep leg vein thrombosis and/or pulmonary embolism, often relied on invasive and costly imaging techniques, such as IV venography and pulmonary angiography. As VTE was confirmed in only about one third of patients in whom it was suspected [144, 145], the development of non-invasive exclusionary tests became necessary. D-dimer, a cross-linked fibrin degradation product, is an indicator of coagulation activation and fibrinolysis and can be measured in both whole blood and plasma [146]. More than 25 years ago, D-dimer testing using quantitative enzyme-linked immunosorbent (ELISA) D-dimer assays was found to be highly sensitive for the detection of VTE (sensitivity  $\geq 95\%$ ) [147–149]. Today, a variety of commercial D-dimer assays are available. The main assay categories include quantitative, fully automated rapid ELISA or immunoturbidimetric latex-agglutination assays with a high sensitivity (96%–99%) but a rather low specificity (38%–48%) and qualitative or semi-quantitative latex agglutination and whole-blood point-of-care tests with a moderate sensitivity (69%–85%) but a higher specificity (68%–99%) [146, 150].

Since the 1990s, prospective management studies have demonstrated that it is safe to withhold anticoagulation in patients with a low/intermediate or unlikely clinical probability of VTE based on clinical scores (e.g., Wells scores,

revised Geneva score) and a negative highly sensitive D-dimer test (e.g., rapid ELISA), precluding the need for further imaging [151, 152]. If a less sensitive D-dimer test is used (e.g., whole-blood agglutination assay), it is still safe to withhold anticoagulation in patients with a low or unlikely probability of VTE [151, 153–155]. It has been estimated that by assessing patients according to this strategy, at least a 30% decrease in diagnostic imaging can be achieved in outpatients with suspected VTE, resulting in less waiting time and diminished costs of care [154]. These results have been corroborated by randomised clinical trials [156, 157]. Practice guidelines recommend initial D-dimer testing when evaluating patients with either a low (with either a moderately or highly sensitive D-dimer test) or moderate clinical probability (highly sensitive D-dimer only) of VTE [8, 158]. If the D-dimer test is negative, VTE is considered excluded and no further imaging, such as compression sonography or spiral computed tomography, is necessary. A positive D-dimer should be followed by imaging. As it is not clear whether D-dimer tests can safely rule out VTE in patients with a high clinical probability, initial testing with imaging (without D-dimer testing) is recommended. The Choosing Wisely campaign, launched by the American Board of Internal Medicine Foundation to avoid overuse, recommends not to order computed tomography to diagnose pulmonary embolism without initial risk stratification (pre-test probability and D-dimer tests if low probability) [159].

Despite its potential to avoid imaging, D-dimer testing is hampered by several practical limitations. D-dimer tests suffer from a lack of standardisation, results (and cut-off points) are not comparable between different assays. As the ability to exclude VTE depends on test sensitivity, clinicians should be aware of the specific assay used at their institution and its test performance characteristics [146]. A major problem of D-dimer is the lack of specificity for VTE, leading to a high rate of false positive results. Elevated D-dimer levels can be found in any condition associated with enhanced fibrin formation and fibrinolysis, including surgery, trauma, infection, pregnancy, cancer, myocardial infarction, stroke, atrial fibrillation, inflammatory conditions, and advanced age [146]. For instance, while about one third of unselected outpatients with suspected pulmonary embolism have a negative rapid ELISA D-dimer test (conventional cut-off 500  $\mu\text{g/l}$ ), this proportion decreases to 5% in patients aged  $\geq 80$  years, 11% in patients with cancer, and 4% of inpatients [160–162], which greatly reduces the efficiency and clinical usefulness of D-dimer as an exclusionary test in these populations. The safety of D-dimer testing to exclude VTE in special situations, such as pregnancy or upper extremity deep vein thrombosis, has not been examined in prospective management studies and therefore, the role of D-dimer testing is yet to be determined in such patients.

Although D-dimer testing was originally developed to reduce unnecessary imaging, an increasing use of D-dimer does not decrease or even increases referrals for VTE-related imaging in the real-life setting [163, 164]. Potential underlying reasons are the indiscriminate use of D-dimer because of its easy availability (together with modern imaging techniques, such as multidetector spiral computed

tomography) and a declining tolerance to diagnostic uncertainty [154]. Attempts have been made to resolve this issue by better selecting patients requiring D-dimer testing for pulmonary embolism using explicit clinical criteria (PERC rule) [165, 166]. Recently, to increase the specificity of highly sensitive D-dimer assays in patients aged  $\geq 50$  years, the utilisation of an age-adjusted cut-off value (cut-off = age  $\times$  10) was successfully validated in a large prospective management study [167]. Finally, the clinical value of D-dimer testing in specific populations, such as pregnant women or patients with upper extremity deep vein thrombosis, must be validated in prospective management studies before its use can be recommended in these populations.

### Personalised medicine in inflammatory and infectious diseases

Inflammatory toxins, immunogenic antigens, infectious pathogens, and mediators of the host response all stimulate pro- and anti-inflammatory mediators and coordinate recruitment of immune cells to the acute site(s) characteristic for the diseases. Precursors, mature forms and degradation products of mediators involved, penetrate from the original site of action into the circulation. As surrogate blood biomarkers these substances mirror the extent and severity of the insult. Numerous attempts have tried to correlate these different mediators with the presence and course of disease as diagnostic and prognostic markers.

Like in other disease states, ED physicians face the dilemma of ambiguous clinical manifestations of infectious and inflammatory diseases at emergency presentation. Inflammation-related cognitive impairment may worsen the value of history-taking. Multimorbidity further masks typical textbook signs and symptoms of infections or makes their presence ambiguous [168]. Even in patients with typical bacterial CAP the classical sign of fever is absent in almost half of hospitalised patients [28]. A positive culture result of a bacterial pathogen in bodily fluids is considered ultimate diagnostic proof for bacterial infection or sepsis by many. Indeed, the possibility for resistance testing argues for routine sampling of (blood) cultures and is life-saving in a setting with prevalent multiresistance. Clinicians, therefore, order blood cultures liberally if bacteraemia is suspected, for example when patients have fever, chills, leucocytosis, signs of focal infections, indications of sepsis, or suspected endocarditis prior to starting parenteral anti-microbial therapy. Unfortunately, these criteria are unreliable and clinical prediction rules lack external validity and are complex with use of difficult-to-obtain variables [169]. Hence, only a small proportion (4%–7%) of blood cultures yield true-positive results [169–171]. Of these, as many as half represent contaminants, i.e. false-positives which may unnecessarily expand investigations and extend hospital stay [172]. Hence, ordering blood cultures without appropriate pre-test probability criteria is both wasteful and harmful [173, 174].

In the pre-antibiotic era, mortality from pneumococcal CAP was between 20 and 30% overall, rising to more than 60% for bacteraemic cases [175]. Today with antibiotics, mortality in patients hospitalised for CAP is between 5% to 10%, dependent on co-morbidity [74], and in septic shock

rise still up to 50% [87]. Earlier administration of antibiotic therapy improves outcomes in patients with severe sepsis [60]. The current sepsis guidelines, therefore, have a strong recommendation for administering antibiotics within 1 hour of the diagnosis (or suspicion) of severe sepsis. [62] Yet, not all patients with clinical signs of infection – including SIRS criteria – truly have a bacterial infection in need of antibiotic therapy for cure. Beneficial effects of empiric antibiotic therapy must be weighed against their harmful effects particularly in regard to emergence of drug-resistant bacteria and other drug-related side effects [176]. Biomarkers may allow transformation of bundled sepsis care to more personalised patient management [177, 178]. The recognition over 25 years ago that the host response plays an exquisite role in sepsis led to the definition of sepsis that is still the standard today [62]. Unfortunately, the systemic inflammatory response syndrome (SIRS) variables (i.e., body temperature, heart rate, tachypnoea, white blood count) turned out to be ambiguous, lacking sensitivity, specificity and ease of clinical application [179]. Thus, a gold standard to differentiate bacterial from non-bacterial or non-infectious causes in patients with SIRS does not exist, and thus all observational studies are prone to a potential bias. As long as patients with the slightest suspicion of (bacterial) infection are treated with antibiotics “just to be safe”, all observational diagnostic studies are biased due to the lack of independent comparison with a true gold-standard for a relevant bacterial aetiology in true need of antimicrobial therapy. This dilemma can, unfortunately, not be resolved by meta-analysing a selection of inherently flawed observational studies since most patients in those studies were in fact treated with antibiotics despite the low pre-test probability for an infection [180–182]. Indeed, the potential to change clinical decision making is the most important performance measure for a biomarker. Therefore, randomised intervention studies have to be done in which the anti-microbial therapy is guided by a biomarker and in which the primary measure of efficacy is outcome [176]. If the patient recovers without antibiotics, there was obviously no serious bacterial illness in need of antimicrobial therapy. Herein, we discuss the two biomarkers CRP and PCT for which several randomised intervention studies have been published. CRP has become a *de facto* “universal inflammatory screening marker” in clinical routine (table 1). Considering the greater sensitivity and specificity demonstrated in an impressive body of literature PCT can reduce the limitation of the SIRS staging in sepsis and improve guidance of anti-microbial therapy [177]. Although far from being a perfect marker [180], PCT improves the accuracy of the clinical diagnosis in hospitalised patients with infections of the respiratory tract and sepsis [28, 35, 183]. In contrast to CRP and other biomarkers, circulating PCT levels are not affected by steroid co-medication [184, 269]. Accordingly, it has been included in the PIRO staging system for sepsis, which includes the predisposition, infection, response and organ failure [185].

### Detection of subtle, sub-acute inflammation with C-reactive Protein (CRP)

CRP is an acute phase reactant whose synthesis in the liver is up-regulated by IL-6 in response to inflammation inde-

pendent of the aetiology. CRP has a role in the clearance of dying and altered cells, and might also have more complex immuno-modulatory functions. Recent evidence suggests that the genetic variants influencing basal CRP level also influence the magnitude of the acute-phase rise in CRP level in active inflammation. These genetic effects might be large enough to directly influence clinical decision-making processes that are based on an interpretation of CRP thresholds [14, 186].

As a biomarker CRP has been used for decades in Europe to screen for the presence of significant inflammatory or infectious disease in the ED [187]. Its advantages include the relatively low pricing in routine labs, widespread availability also for general practitioners as point-of-care tests and high sensitivity even for low grade and chronic systemic inflammation.

Indeed, as a sensitive marker of subtle, sub-acute vascular systemic inflammation, measurements of high-sensitivity CRP (hs-CRP) plasma levels add to both the prognostic information gleaned from assay of plasma lipid risk factors and the risk levels estimated by means of Framingham study-based criteria [188–190]. A large-scale, randomized clinical trial – Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) – demonstrated that potent statin therapy reduces the risk of heart attack and stroke by 50% among men and women with low levels of LDL-cholesterol who are at increased vascular risk mirrored by elevated levels of CRP [191].

Every year there are millions of visits to primary care physicians by adults with a chief of complaint of cough, representing over 5% of all visits to physicians. To determine the aetiology of infections of the respiratory tract history and prescribe antibiotic therapy, history and physical examination are misleading [28, 31, 35], which leads to antibiotic over-prescription “just to be safe”. In acute bronchitis, the antibiotic prescription rate should be zero. Despite years of intensive and internationally concerted efforts, in the US the rate hovers around 70% both in primary care and EDs. [192] Factors such as diagnostic ambiguity about possible bacterial infection, avoidance of potential risks with legal consequences, and patient demands play an important role. Prescription rates of antibiotics was lowered in a study-setting by around 10% by a clinical decision support system [193]. Unfortunately, this effect is only modest and not persistent. Together with measures to enhance communication-skills of general practitioners as point-of-care test CRP reduced antibiotic overuse in mild and usually self-limiting respiratory tract infections by 30 to 40% [194, 195].

Unfortunately, in more poly-morbid and severely ill, and thus more inflamed patients admitted to the ED, CRP tended to increase antibiotic prescriptions for acute cough illness when compared to a clinical algorithm [196]. A low specificity, delayed dynamics and attenuated rise by concomitant steroid medication are important drawbacks of CRP as a biomarker in systemic and more peracute infections (sepsis) especially in the presence of poly-morbidity, which is omnipresent in hospitalised patients [84, 197]. Many physicians use it in hospitalised patients for the follow up of infectious diseases, despite CRPs drawbacks

and misleads as marker, for example in LRTI admitted to the ED, [117] hospitalised CAP [28, 105], COPD [198] or sepsis [104].

Despite these limitations in the hospital setting, CRP is bundled in countless “admission labs”. This despite the lack of any guidelines to recommend this (mis-)use and no consequences for the decision-making or therapeutic process. Once established as a “standard of laboratory care” for admission and hospital follow-up, it is almost impossible to not use it in clinical routine. As a contagious laboratory disease artefact this leads directly or indirectly to additional investigations to differentiate the alleged “*CRPitis*”. This exemplifies the dilemma for biomarkers, that we are rapid in adopting new measures but reluctant to stop measuring them once we have got used to it. Another potential target for the “choosing wisely” of the American College of Physicians campaign?

### **Procalcitonin to de-escalate anti-microbial treatment and sampling of blood cultures in infections of the respiratory tract and sepsis**

In systemic infections, calcitonin (CALC) genes are ubiquitously expressed in parenchymal cells and, in essence, the entire body becomes an endocrine organ [90, 199]. PCT, a CALC-I gene product, is stimulated synergistically by the inflammatory mediators of host response (e.g., interleukin (IL)-1 $\beta$ , tumour-necrosis factor (TNF)- $\alpha$ , and IL-6), bacterial products (e.g., [LPS (lipopolysaccharide)], lipoteichoic acid) and necrotic body cells [81, 199–202]. This typically occurs following external infection with bacterial micro-organisms. Bacterial translocation triggered across the gut wall by gastrointestinal malperfusion may trigger a similar cascade, which explains why circulating PCT increase both during septic and cardiogenic shock [203, 204]. PCT is the prototype of a *hormokine* mediator, sharing biological characteristics of both, hormones and cytokines [83, 205]. It circulates as 114 amino acid, lacking the N-terminal dipeptide alanine-proline [90]. Historically, a hormonal function of calcitonin peptides was alluded to calcium homeostasis and bone metabolism [90, 206, 207]. Today, they are thought to adapt metabolism and vascular tone to acute needs in inflammation [81, 93], to combat invading microbes during exogenous infections [208], to modulate migration and phagocytic activity of neutrophils, and to locally increase in pro-inflammatory cytokines and NO [90]. PCT modulates the action of other members of the calcitonin peptide superfamily, including CGRP (calcitonin gene-related peptide), ADM (adrenomedullin) and amylin [88]. The several 100'000-fold increased PCT levels nullify their activities, effects that likely are beneficial in this illness. Accordingly, administration of recombinant PCT protein to septic hamsters with peritonitis doubled their death rate [209]. Conversely, treatment with antiserum reactive against calcitonin precursors increased survival in mono- and polymicrobial sepsis in three animal models (hamster, rats and pigs) [209–212].

Unfortunately, PCT (aka “immune-reactive calcitonin”) was initially propagated as a dichotomous diagnostic and prognostic biomarker for critically-ill patients with pancreatitis [213] and toxic shock syndrome associated with hypocalcaemia, [214] burns and lung injury [215, 216], men-

ingitis in children [217, 218], neonatal infections [219] and adult sepsis in intensive care units [87, 220, 221]. Superior to other biomarkers, PCT appeared to improve the clinical diagnosis of sepsis in critically ill patients [183]. At that time, sepsis was ill-defined as the presence (probable or documented) of infection together with systemic manifestations of inflammation [62, 179]. The consequent ambiguities in interpretation of different cohorts and settings precluded an undisputed sentence on the utility of PCT in the intensive care setting [180, 197, 222, 223]. PCT's kinetic profile shows a prompt increase within 6–12 hours of infection and circulating PCT levels are cut in half daily when the infection is controlled [224]. PCT correlated with bacterial load [171, 173, 225] and severity of infection and outcome [226–228]. PCT offers additional prognostic information in high-risk patients as an adjunct to existing rules [229]. An increase of PCT suggested early identification of moribund critically ill patients despite being on antibiotic therapy [230]. A subsequent large ICU based multicentre PASS-trial, however, documented deleterious effects when antibiotics and diagnostic measures were *escalated* based on increasing PCT levels >1 ng/ml in patients for whom infection may not have been the main problem necessitating ICU admission [231]. In this study, measurement PCT was delayed as samples had to be shipped hundreds of kilometres to a central study laboratory. Protocol-driven there were more investigational procedures, increased side-effects of intensified antibiotic treatment and organ-related harm resulting in a prolonged stay in the intensive care unit [231]. The antibiotic *escalation* strategy like the one used in the PASS-trial can definitely not be recommended in a setting with a high baseline antibiotic exposure, such as an ICU in Denmark [232].

Conversely, a more rational antibiotic *de-escalation* strategy in critically-ill patients with suspected sepsis syndrome on antimicrobial therapy using adapted cut-off ranges proved to be safe and effective with 25% reduction of antibiotic exposure in the large multicentre PRORATA study in France [233].

To date, the efficacy and safety of PCT protocols to *de-escalate* antibiotic overuse has been demonstrated in more than 14 randomised, controlled trials in different clinical settings and including infections of varying severity [177, 234, 235]. The respiratory tract is the most common original site of bacterial sepsis [87]. Over 90% of all respiratory infections are initially presumed to be of single or even multiple viral origin [236]. Interestingly, cellular up-regulation of PCT is attenuated by cytokines released in response to viral infections, such as interferon-gamma (INF- $\gamma$ ) [201]. ICU studies including patients with only viral or both viral and bacterial CAP during the H1N1 outbreak found higher PCT levels in the latter group [237–239]. The PCT *de-escalation* protocols used were similar and all based on the same intuitive concept: recommendations for or against initiation or continuation of antibiotic therapy was based on initial PCT levels, the kinetics of PCT over time, or both, as well as the clinical picture of the patient [74]. The cut-off ranges differed depending on the clinical setting and the acuity of presentation [234]. These protocols proved to be safe and highly effective in terms of lowering antibiotic exposure. In fact, for low-severity pa-

tients, such as bronchitis and upper respiratory infections in general practice, prescription rates lowered by 60%–70% were found [177, 234, 235]. In the ED, antibiotic initiation was reduced by almost 50% in severe lower respiratory tract infections and 60% in severe exacerbations of COPD patients with need for hospitalisation [240, 241]. Of note, all these studies were done in settings with a very low antibiotic prescription rate in the control group. Thus, the effect would even more pronounced in countries with higher antibiotic exposure and resistance rates. In higher-severity patients, PCT guidance resulted in a relative reduction in the duration of antibiotic treatment by 40% in CAP and by 25% in the critical care setting [233, 242]. PCT-guide *de-escalation* of empirical antibiotic therapy resulted in lower medication costs, antibiotic side effects and adverse outcomes [5, 74].

Can these data, mostly obtained in hospitalised patients with respiratory tract infections, be indiscriminately applied to other sites of infection, to all age groups or sepsis in general? Clearly, NO! Community-acquired respiratory tract infections are relatively homogenous; a prerequisite that the procalcitonin algorithm actually worked. Indeed, “sepsis” is merely an ill-defined, heterogeneous clinical syndrome [243]. PCT can merely complement a physician and the clinical judgment on the probable site and source of infection will always remain a fundament for patient care. Therefore, the host response and optimal cut-off ranges for PCT vary with underlying illness, co-morbidity and immune status of the patients as well as the source and virulence of initial infection, such as meningitis, endocarditis, abdominal, urinary tract, catheter related or nosocomial infections [46]. Cut-off ranges have to be calculated by multilevel likelihood ratios and adapted to different settings and types of infection. Rapid and appropriately sensitive assays are to be used [45, 46, 244].

For example, the cut-off used in adults has been shown to be too low for children with a more reactive immune system [245, 246]. In new-borns there is even a physiological rise within the first postnatal days, presumed to be associated with intestinal bacterial colonisation [247, 248]. If the cut-off is adapted accordingly, PCT becomes a reliable marker to diagnose neonatal infections [249]. In a pilot-study from France, a PCT level of <0.5 ng/ml was used to avoid unnecessary antibiotics and hospitalisation in children during an outbreak of viral meningitis [250].

PCT reflects severity of renal lesions in pyelonephritis [251] and bacteremia and bacterial load and in the urosepsis syndrome [225]. Guidelines on the duration of antibiotic therapy are largely based on expert opinion only, therefore infections of the urinary tract are another target for PCT-guided stewardship [252]. Indeed, together with the resolution of pyuria [253], Combined pyuria and PCT guidance led to a 40% reduction of mean antibiotic exposure in a recent randomised pilot study [254].

In patients with suspected bloodstream infections, the aetiology of a presumed “bacterial” cause of fever cannot be detected in 50–80% [171, 173, 174, 255]. Clinicians order blood cultures liberally in patients admitted for CAP in the ED though they are costly and less than 5% of blood cultures yield true-positive results which change anti-microbial therapy [169]. PCT levels on admission accurately



predict later blood culture positivity in immunocompetent patients with CAP. A PCT cut-off of 0.1, 0.25 or 0.5 mg/l would enable reduction of the total number of blood cultures by 13, 37 or 52% and still identify 99, 96 or 88%, respectively of positive blood cultures in CAP [171]. These figures are superior to clinical decision rules, which have practical limitations like the need for complex calculations and memorising [256]. As many as half of the positive cultures represent contaminants – organisms (usually coagulase negative staphylococci) inoculated from the skin at the time of sample collection. False-positive blood cultures expose patients to potential harm like additional diagnostic testing (additional blood cultures, echocardiograms, etc.), unnecessary antibiotic administration, missed alternative (infectious or non-infectious) diagnoses and prolonged hospitalisation [169]. PCT also seems to differentiate contaminants from true positive blood cultures [173]. In summary, PCT is the most reliable of the currently known circulating markers of systemic bacterial infections (“sepsis”); it is the only one that correlates well with its presence, course, and outcome in humans. PCT-guided antibiotic *de-escalation* therapy is considered evidence-based state-of-the-art in respiratory tract infections and recommended by updated guidelines [62, 257]. The hypothesis that hormokines are not only biomarkers but have a pivotal role in the pathophysiology of sepsis is at the least attractive, and at best intuitively obvious.

## Epilogue

“With the rapid extension of laboratory tests of greater accuracy, there is a tendency that for reaching a final diagnosis clinicians and students rely more and more on laboratory reports and less on the patients history, the examination and behaviour of the patient, and clinical judgment. While in many cases laboratory findings are invaluable for reaching correct conclusions, the student should never be allowed to forget that it takes a man, not a machine, to understand

a man.” A seemingly contemporary statement from 1946! [258].

Some decry the loss of clinical skills with history taking and physical examination in routine patient care. Others suggest that emphasis on clinical skills is from a bygone era and that the availability of advanced imaging techniques and laboratory tests have supplanted ambiguous history and physical findings [26]. As usual, both extremes are irrational. The allegedly infallible impact of proper history and clinical exams in “the good old days” might appear nostalgic and outdated if applied to the more complex and diversified differential diagnostic spectrum and therapeutic options of modern medicine. Conversely, over-reliance on the new procedures contributes directly to misdiagnosis. Too often, palpably illogical laboratory findings are accepted without question [259]. Technology is an adjunct to clinical judgment and should not become a “gold standard” for diagnosis alone.

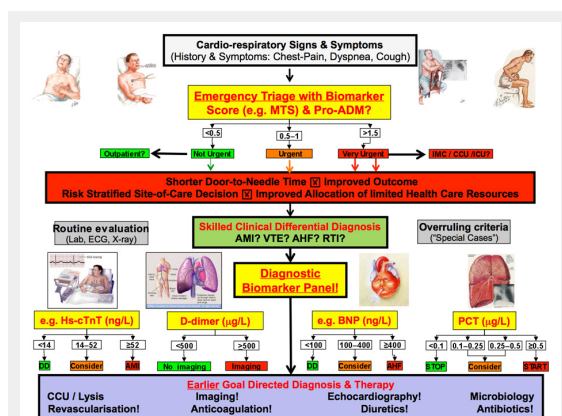
Proper risk stratification with biomarkers helps caregivers to more appropriately direct diagnostic, monitoring, or therapeutic interventions. Adverse events due to delays are a major contributor for adverse hospital outcome. In a busy emergency room, however, it is difficult or even impossible to identify patients in whom harm would have been prevented by more aggressive intervention. Substantial evidence exists for many conditions – sepsis for example – showing that earlier and more targeted intervention can improve patient outcomes, especially with the use of protocols or guidelines. Selected diagnostic and prognostic biomarkers should and will have a more prominent role in future emergency triage [260]. More personalised, better-targeted healthcare resource application offers opportunities to improve timeliness, safety, efficacy, and cost-effectiveness of care, as well as quality-of-life of patients and their loved ones. Rationalising for prevention of rationing is the *credo*!

The future of biomarkers lies in intervention studies across heterogeneous populations in combination with clinical scores and close to “real-life” settings. Comprehensive effectiveness research studies are being carried out aiming to further validate these concepts in “real-world-settings” and thereby improve patient care [261]. Results of these trials may ultimately help to transition from bundled treatment strategies to more individualised patient care thereby providing better, hopefully still empathic, management for the allocation of limited patient and societal resources (fig. 4).

Finally, as physicians we should always be aware that, before and after all, a patient is a human being seeking help. After we have tried to explain to him all the medical progress, fancy biomarkers for personalized diagnosis and novel options for individualised therapy, we might be puzzled by the question of the patient “Personalised medicine, doctor, does this mean that you have more personal time for taking care of me?”

## Key issues

- Every medical therapy in emergency care has potential adverse effects and expedited selection of patients most likely to benefit is crucial, making more personalised approaches necessary.



**Figure 4**

Personalised clinical and biomarker-guided medicine in the emergency department.

POC = point of care; MTS = Manchester Triage Score; ProADM = proadrenomedullin; ICM = intermediate care; CCU = coronary care unit; ICU = intensive care unit; Lab = laboratory analysis of biomarker level; X-ray = chest radiography; ACS = acute coronary syndrome; AHF = acute heart failure; RTI = respiratory tract infections; hs = highly sensitive; DD = differential diagnosis

- Specific blood biomarkers may allow transition from generalising care bundles to a more tailored management in individual patients thereby reducing the risk for adverse treatment outcomes in patients who – based on their biomarker levels – do not likely benefit from therapy.
- Biomarkers measured on admission and during follow-up can support the clinician's early recognition of cardiorespiratory, inflammatory and infectious diseases, severity assessment with adequate site-of care decisions and most effective therapeutic decisions in individual patients.
- Proadrenomedullin (ProADM) is an inflammatory prognostic marker that improves early mortality prediction and might improve site-of-care decisions, as tested in patients with respiratory infections.
- Initial D-dimer testing should be done when evaluating patients with either a low (with either a moderately or highly sensitive D-dimer test) or moderate clinical probability (highly sensitive D-dimer only) of venous thromboembolism (VTE). If the D-dimer test is negative (e.g. cut-off <500 µg/l) VTE is excluded, without the need for further imaging.
- Cardiac troponin I and T are quantitative markers of cardiomyocyte injury and indispensable tools in the early diagnosis of AMI.
- Natriuretic peptides are quantitative markers of hemodynamic cardiac stress and indispensable tools in the early diagnosis of acute heart failure
- C-reactive protein (CRP), as marker for more subtle sub-acute inflammation has a role in the risk selection for statin therapy in primary prevention of cardiovascular diseases.
- Procalcitonin (PCT) algorithms facilitate assessment of bacterial infection risk and appear to be safe in guiding therapeutic decisions about initiation and duration of anti-microbial therapy in infections with respiratory origin regarding the results from interventional trials.

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## Figures (large format)

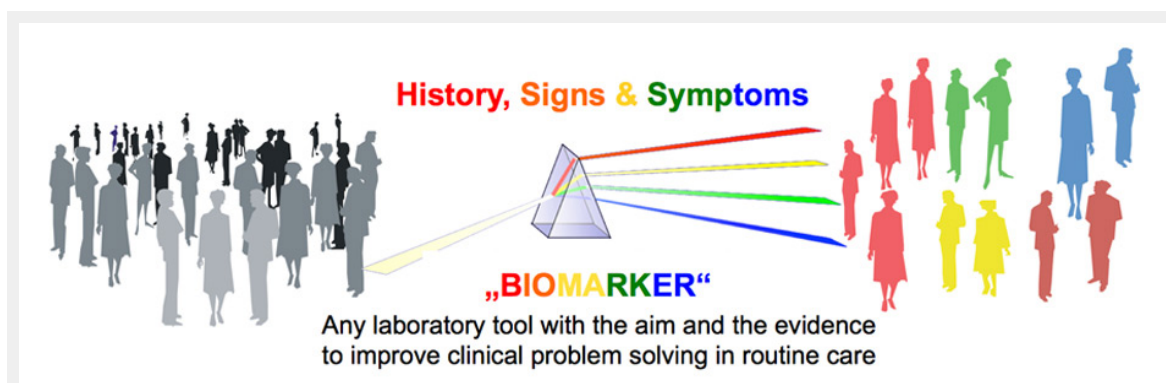


Figure 1

Combined clinical and biomarker assessment for a personalised emergency triage, therapeutic intervention and site of care decisions.

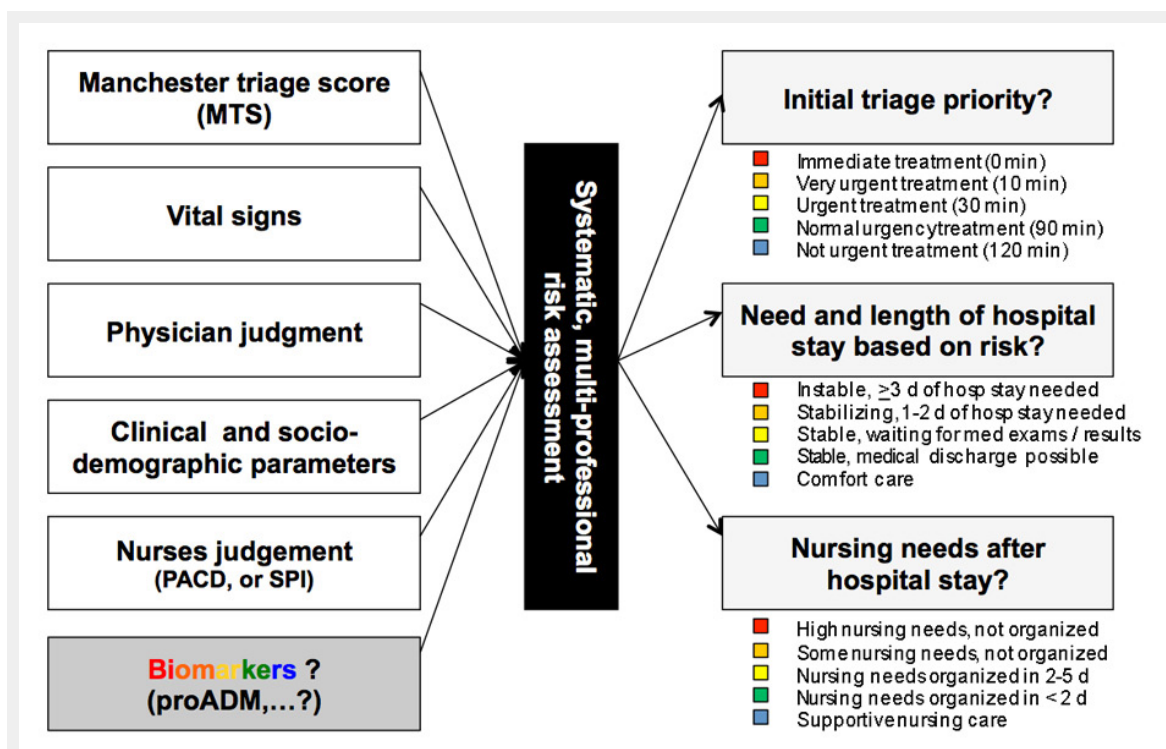


Figure 2

Systemic multiprofessional risk assessment for improve patient management adapted from [261].

ProADM = proadrenomedullin

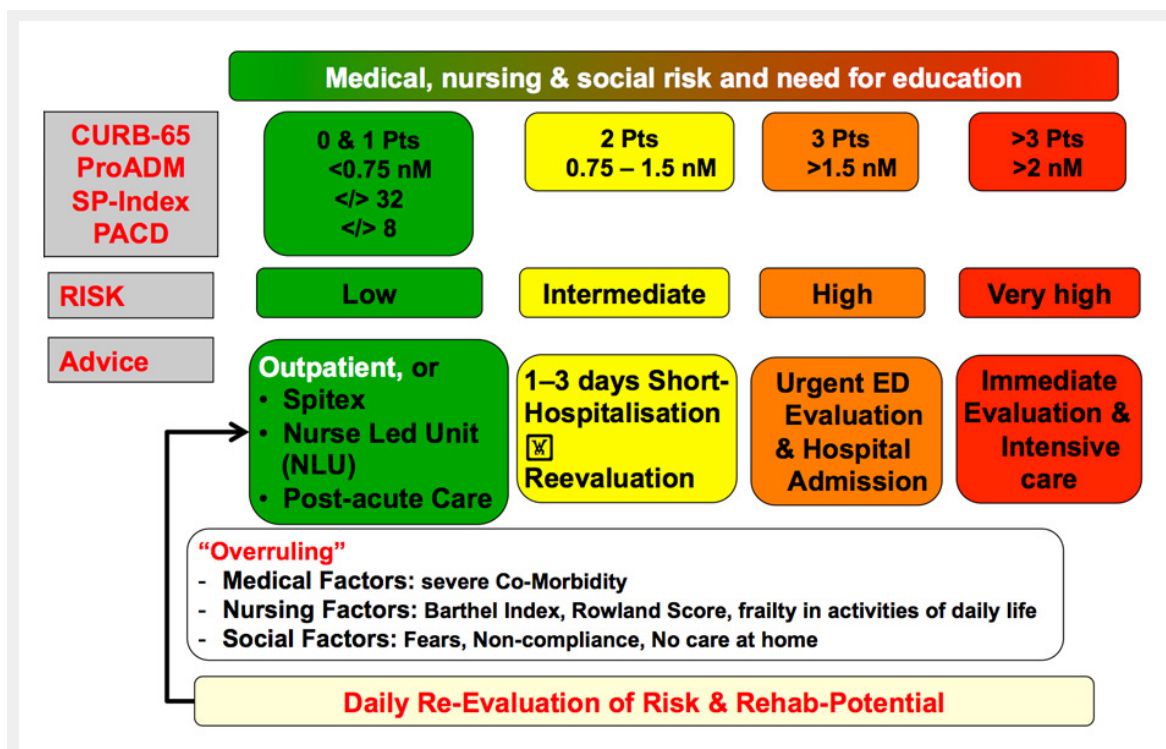


Figure 3

CURB-A score combining the traditional CURB-65 criteria with levels of proADM to risk stratify site-of-care decisions in patients with lower respiratory tract infections.

ICU = intensive care unit; ProADM = pro-adrenomedullin; SP = Selbstpflege (self-care); PACD = post-acute care discharge

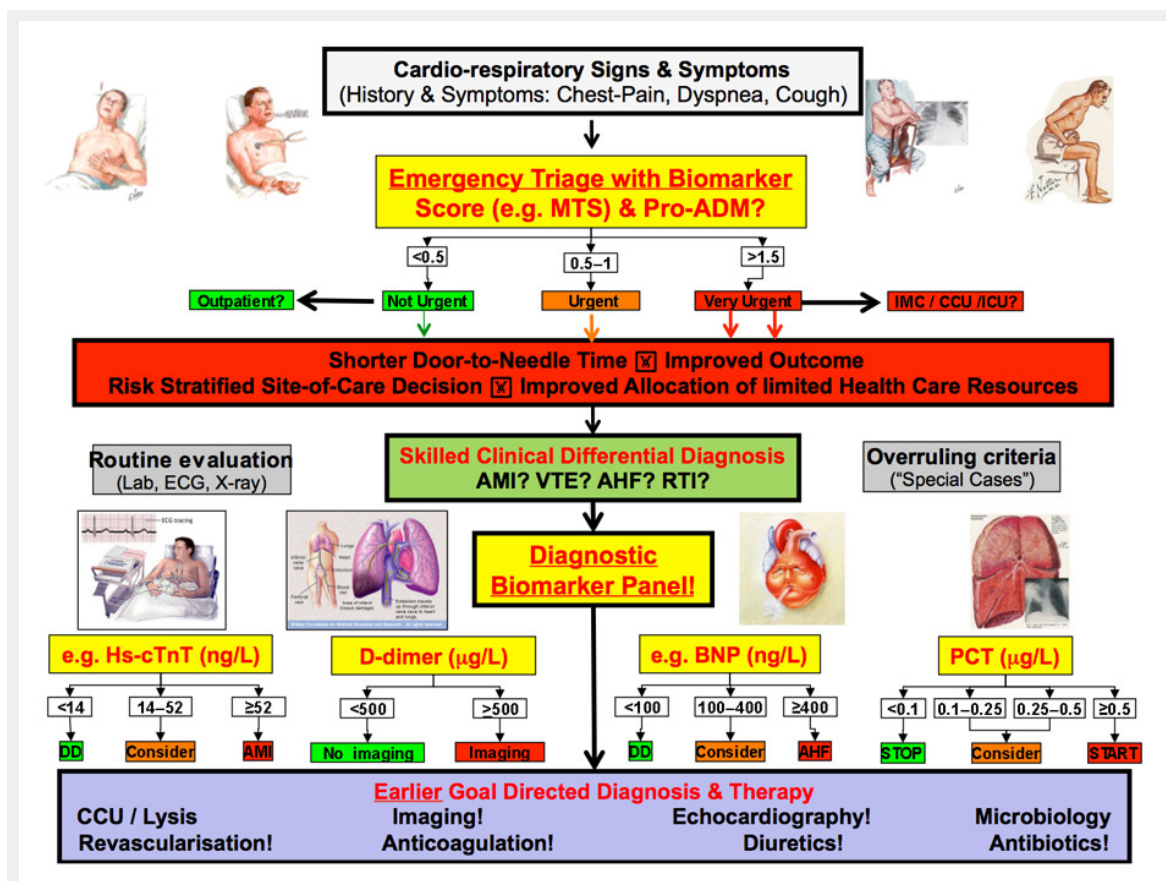


Figure 4

Personalised clinical and biomarker-guided medicine in the emergency department.

POC = point of care; MTS = Manchester Triage Score; ProADM = proadrenomedullin; ICM = intermediate care; CCU = coronary care unit; ICU = intensive care unit; Lab = laboratory analysis of biomarker level; X-ray = chest radiography; ACS = acute coronary syndrome; AHF = acute heart failure; RTI = respiratory tract infections; hs = highly sensitive; DD, = differential diagnosis